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Physical activity and sleep in patients with hypermobile Ehlers–Danlos syndrome and patients with generalized hypermobility spectrum disorder

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ABSTRACT

Aims: Research objectively evaluating physical activity (PA) and sleep in adults with hypermobile Ehlers–Danlos syndrome (hEDS) and generalized hypermobility spectrum disorder (G-HSD) is lacking. Furthermore, it is not clear to what extent frequently occurring symptoms in these patients are related to their PA and sleep. Therefore, a cross-sectional study was performed to objectively evaluate, and identify factors contributing to, PA and sleep in adults with hEDS and G-HSD.

Methods: Twenty female adults with hEDS, 23 with G-HSD, and 32 healthy controls participated. Physical activity and sleep were measured using two tri-axial ActiGraphs worn over seven consecutive days. Furthermore, questionnaires evaluating frequently occurring symptoms were completed. Regression analysis was performed to determine major contributors to PA and sleep.

Results: Daily step counts were significantly lower in both patient groups compared to the control (CTR) group ($p<0.04$) and to the recommended 7500 steps ($p\leq0.001$). Other PA and sleep variables did not differ between the groups. In the hEDS group, body mass index and kinesiophobia were related to PA, explaining 53% of the variance in step counts. In the G-HSD group, 18.5% of the variance in step counts could be attributed to the variance in pain impact.

Conclusion: Adults with hEDS and G-HSD had lower step counts than healthy peers, which may be partially due to kinesiophobia and the impact of pain respectively. No differences in objectively measured sleep parameters were identified. Treatment focusing on fear-avoidance beliefs and pain relief could potentially increase daily step counts and benefit overall health in these patients.

Keywords: Hypermobile Ehlers–Danlos syndrome, Hypermobility spectrum disorder, Physical activity, Sleep

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INTRODUCTION

Ehlers–Danlos syndrome (EDS) is a hereditary connective tissue disease caused by mutations in genes encoding for fibrillary collagens or their modifiers, resulting in hypermobility, tissue fragility, and skin hyper extensibility [1, 2]. Previously, six subtypes were distinguished based on the Villefranche criteria of 1997 [1]. Since the identification of numerous mutations in an array of novel genes, the EDS classification was revised in 2017, now covering 13 subtypes of which the hypermobile type of EDS (hEDS) is the most common [2]. However, as the genetic basis of hEDS remains unknown, diagnosis is based on clinical criteria, which include generalized joint hypermobility (GJH) and chronic pain, as well as signs of soft tissue fragility such as organ prolapse, atrophic scarring, aortic root dilatation, mild skin hyperextensibility, and multiple abdominal hernias [2]. Patients with joint hypermobility not meeting the criteria for hEDS are currently diagnosed with hypermobility spectrum disorder (HSD), of which the generalized subtype (G-HSD) is characterized by GJH with secondary musculoskeletal symptoms. These symptoms include musculoskeletal or soft tissue traumas, chronic pain, reduced proprioception and muscle strength, and other musculoskeletal traits caused by the interaction between the affected musculoskeletal tissues and mechanical forces [3].

Joint instability, recurrent joint dislocations, poor proprioception, reduced muscle strength, and fear of movement have been postulated as potential causes for reduced physical activity, which is a common feature in patients with GJH [4–7]. Besides a lower habitual PA and sport activities level, poor PA levels were identified with 50% of the patients with GJH being inactive [5, 8–10]. In turn, reduced physical activity may lead to impaired sleep quality in hEDS/HSD, as these are bidirectionally related in the general population [11–13]. Moreover, impaired sleep quality has been observed in patients with symptomatic GJH, reflected as a higher prevalence of obstructive sleep apnea and snoring, problems of maintaining sleep and not feeling refreshed in the morning [14, 15]. Gaisl et al. (2017) have shown that these sleeping problems have a major impact on their health-related quality of life [16]. Furthermore, frequently occurring symptoms such as pain and fatigue compromise sleep and PA, resulting in a vicious circle of activity limitations and impaired quality of life [5, 7–9, 17–20].

There is overwhelming evidence of the health benefits of regular PA and good sleep quality in healthy individuals and patient populations, such as a reduced mortality and reduced incidence of several chronic medical conditions (e.g., cardiovascular diseases, hypertension, and several cancers) [21–23]. However, studies measuring PA and sleep in a hypermobile and EDS population are scarce and mainly based on self-report questionnaires, which are known to likely result in misclassification due to participants providing socially desirable responses. Furthermore, previous reports included patients with generalized hypermobility diagnosed according to the older and less strict diagnostic criteria [1]. Moreover, it is not clear to what extent frequently occurring features such as fatigue, pain, anxiety, and depression are related to PA and sleep in these patient populations. Therefore, this study aims to objectively evaluate PA and sleep (using tri-axial accelerometry) of adults with hEDS and G-HSD diagnosed according to the new diagnostic criteria, and compare this to the PA and sleep of healthy controls and recommended values. The major contributors to PA levels and sleep quality of individuals with hEDS and G-HSD will also be examined. We hypothesize that, based on the clinical profile of both patient groups, PA and sleep are impaired in comparison with the healthy controls and associated with typical features such as pain and fatigue.

MATERIALS AND METHODS

Participants

This study protocol was reviewed and approved by the Ethical Committee of Ghent University Hospital (EC number 2017/1311), and written informed consent was obtained from all participants. Recruitment and data collection were performed between November 2017 and March 2019. Twenty female individuals with hEDS and 23 with G-HSD, aged between 18 and 65 years, were recruited from the Center for Medical Genetics of Ghent University Hospital. Exclusion criteria were pregnancy, recent surgery of the lower extremity, and any current neurologic or orthopedic conditions unrelated to hEDS/G-HSD affecting balance or gait. Furthermore, 32 female healthy controls individually matched to both patient groups for age (± 3 years) and body mass index (BMI; ± 2 kg/m^2) were recruited through social media and flyers. They were included in this study, if they—in addition to the exclusion criteria for the patient groups—did not have GJH, measured by a Beighton score of 5/9 or more in adults <50 years old and 4/9 or more in adults ≥50 years old. The Beighton score is a reliable screening tool consisting of nine tests, of which age-dependent cut-off scores (as above) indicate generalized joint hypermobility [1, 24].

Procedure

Participants were invited by e-mail or phone to participate in this study at Ghent University Hospital. Participant characteristics, including hypermobility (Beighton score), BMI, height (digital scale), weight (stadiometer), profession, current working status, education, marital status, and age (questionnaires) were evaluated. All participants were enrolled in the study for one week in autumn or winter to control for

seasonal effects on PA [25]. During this week (i.e., 7 days) participants were asked to complete questionnaires every evening to evaluate their pain, analgesic medication, sleepiness, mood, and fatigue, while also wearing tri-axial accelerometers to measure their sleep and PA. At the end of the test week, surveys evaluating quality of life (QoL), kinesiophobia, and the psychosocial impact of pain were completed.

Physical activity and sleep measurements

Physical activity and sleep were measured using two tri-axial ActiGraphGT3X-BT accelerometers (ActiGraphTM, LLC, Pensacola, FL, USA). One ActiGraph was worn on the right hip (midaxillary line at the level of the iliac crest) to measure PA, a procedure previously shown to be valid [26]. The other ActiGraph was worn on the dominant wrist to score sleep. This has previously been shown to have high sensitivity, moderate specificity, and overall high accuracy [27, 28]. Participants were instructed to wear these directly on the skin 24 hours a day during seven consecutive days, except for water-based activities [29].

Data were recorded at a frequency of 90 Hz, as these sampling frequencies produce more accurate estimates [29]. Data were only included in the PA analysis if four or more valid days with ≥ 8 hours of wearing time during waking hours (i.e., 7:00 AM–10:00 PM) was achieved [30]. Non-wear time was defined as 60 minutes of consecutive zero counts per minute (cpm), without interruptions in counts [31]. For sleep analysis, reported bedtime ('when did you try to go to sleep?') and wake time ('when did you wake up?') of each participant was used to identify sleep periods. Participants were included in sleep analysis when having at least four nights of sleep data. Epoch lengths (1 s for PA and 60 s for sleep analysis), cut-points and algorithms of PA and sleep were based on previously published validation studies [32, 33].

Daily step count was retrieved as main PA outcome. As secondary PA outcomes, PA was categorized in four categories based on intensity: daily minutes spent in moderate (vector magnitude = 2690–6166 cpm), vigorous (vector magnitude = 6167–9642 cpm), very vigorous (vector magnitude ≥ 9643 cpm) and, combining moderate, vigorous and very vigorous activity minutes together, moderate to vigorous physical intensity (MVPA) [32]. The following sleep parameters (during the night) were determined: total sleep time (min), total bed time (min), sleep efficiency (main sleep outcome as the percentage of total sleep time divided by total bed time), wake after sleep onset (WASO, amount of time in minutes awake after sleep commenced and before final awakening), latency (time in minutes from bedtime to first sleep bout), and overall number of awakenings [33]. All parameters were analyzed with ActiLife 6 software. For each participant, the mean of these parameters on all valid days (PA) or nights (sleep) was calculated.

Patient-reported outcomes

All participants were asked to complete a series of questionnaires. The outcomes that were reported by the participants and used in analyses are shown in Table 1 [34–50]. Six questionnaires were completed on a daily basis, of which the mean of all days was calculated and included in the analysis. Three questionnaires were filled in at the end of the week and results on weekly basis were included in analysis.

Table 1: Patient-reported outcomes

Outcome	Questionnaire	Frequency	Construct	Range scores + interpretation	Psychometric properties
Painful body area	Margolis pain diagram (34)	Daily	Color painful body areas on a diagram	Total scores: 0–100% Higher scores: larger total painful body surface	High test-retest reliability coefficient in chronic pain patients: r=0.85 (35)
Number of doses pain medication taken	Self-constructed question	Daily	/	Higher scores: higher number of doses pain medication (any type) taken	/
Daytime sleepiness	Epworth Sleepiness Scale (ESS) (36,37)	Daily	Eight questions about the chances of falling asleep in different situations, ranging from 0 (no chance of dozing) to 3 (high chance of dozing)	Total score: 0 (no daytime sleepiness) to 24 (excessive daytime sleepiness)	Moderate validity and high IC (α=0.88) in patients with sleep disorders (37,38)

Table 1: *(Continued)*

Outcome	Questionnaire	Frequency	Construct	Range scores + interpretation	Psychometric properties
Subjective sleep quality	Self-designed questions: (1) 'how well did you sleep last night?', (2) 'How often did you wake up last night?' and (3) 'How well recovered did you feel on waking this morning?'	Daily	Three questions ranging from 0 to 6: (1) 0 = excellent, 6 = very poorly (2) 0 = not once, 6 = a lot (3) 0 = completely, 6 = not at all	Total score: 0 (excellent) to 18 (very poorly)	/
Affective distress	Hospital Anxiety and Depression Scale (HADS) (39)	Daily	Seven questions about anxiety and seven about depression, ranging from 0 to 3	Anxiety: 0–21 Depression: 0–21 Higher scores: more affective distress	High IC (mean α for anxiety: 0.83, α for depression: 0.82), moderate to high validity in patients with anxiety/ depression (40)
Fatigue	Checklist Individual Strength (CIS) (41, 42)	Daily	20 questions, four subscales: subjective fatigue, reduction in motivation, in activity and in concentration	Total CIS score (summation of all subscales): 20–140 Higher scores: higher degree of fatigue, impaired motivation, less activity and concentration problems	High IC (α=0.84–0.95), moderate to high validity in healthy people, cancer survivors and patients with CFS (43)
Health-related quality of life	RAND 36-item Health Survey (SF36) (44)	End of the week	Eight domains: (1) physical functioning, (2) bodily pain, (3) role limitations due to physical problems, (4) general health perception, (5) social functioning, (6) general mental health, (7) vitality, and (8) role limitations due to emotional problems. Raw scales were linearly converted to a 0 to 100 scale	Physical (PCS; domain 1–4) and mental (MCS; domain 5–8) health component summary score: 0–400 Higher scores: higher levels of well-being or functioning	High IC (Mean α across scales = 0.84), moderate to high validity in healthy population, migraine patients and cancer patients (44)
Fear of movement and fear of (re)injury	TAMPA scale for Kinesiophobia (TSK) (45,46)	End of the week	17 questions, ranging from 1 (strongly disagree) to 4 (strongly agree)	Total score: 17–68 Higher scores: higher degree of kinesiophobia	Acceptable to good IC (α=0.79-0.81) in patients with chronic low back pain/FM, moderate validity in patients with acute low back pain (47,48)
Psychosocial impact of pain	Multidimensional Pain Inventory (MPI) (49)	End of the week	Only part one (pain-relevant psychosocial aspects) was included. Five subscales: pain severity, interference with the daily life due to pain, perceived life control, affective distress and social support	Total score (accumulation of mean scores on each subscale): 0-30 Higher scores: higher psychosocial impact of pain	Acceptable to good IC (α=0.74–0.89) in patients with FM/ back pain, good validity in patients with chronic pain (49,50)

r: correlation coefficient, α: Cronbach's alpha, CFS: chronic fatigue syndrome, FM: fibromyalgia, IC: internal consistency.

Statistical analyses

Data analysis was performed using the statistical package SPSS version 25. Missing data (<8% for all outcomes) were excluded from analysis. Normality was evaluated by the Shapiro–Wilk test and visual inspection of the Q-Q plots. Data are shown as mean ± SD (normal distribution) or medians and quartiles. Parametric univariate analysis of variance (ANOVA) analyses were performed to compare questionnaire outcomes and PA and sleep outcomes between the three groups. For all variables, statistical assumptions for the univariate ANOVA analysis were fulfilled, except for total sleep time and checklist individual strength (CIS) in which a Welch ANOVA was performed. When significant differences were identified, a post-hoc Tukey test was performed. Other continuous data (non-normally distributed) were compared between the three groups (hEDS, G-HSD, and CTR group) by a non-parametric Kruskall Wallis test, after which a pairwise comparison was performed (Dunn–Bonferroni) if significant differences were observed. Categorical parameters were compared between groups by a Fisher exact test. Additionally, a one-sample *T* test was performed to compare daily PA (step count) and sleep (sleep efficiency) parameters with recommended values (7500 steps or "somewhat active" and 85% sleep efficiency respectively) [51, 52]. Furthermore, absolute and relative frequencies were calculated of the participants (not) meeting these recommended values.

To identify the relationship between main PA or sleep outcomes (mean step count or sleep efficiency respectively), and patient characteristics (age, BMI, and Beighton score) and patient-reported outcomes, bivariate correlations using Pearson's correlation for normal distributed data and Spearman for non-normal distributed data, were calculated. Afterwards, backward stepwise linear regression analysis was performed with the variables which had a significant association with the main PA or sleep variable [53]. Multicollinearity among the independent variables was checked by computing a variance inflation factor (VIF) of which values above 2.5 were used to indicate a multicollinearity problem in the model. Adjusted *R* square was used to explain the variance in the model. P values less than 0.05 were considered statistically significant.

RESULTS

Participant characteristics

Participant characteristics are shown in Table 2. No significant differences in BMI, age, profession, education, and marital status were observed between groups. Beighton score and pain were significantly higher in the patient groups compared to the controls (all p<0.001). Significantly less participants in the patient groups were working or studying, when compared to the controls. Furthermore, about half of the patients were on sick leave versus none in the CTR group.

Physical activity and sleep

Physical activity and sleep data are shown in Table 3. All participants wore the monitors for a mean of 6.9 valid days with 848.4 minutes of wearing time, with no differences between groups. Mean daily step counts were significantly lower in the hEDS (mean difference –1813 steps, 95% CI –3137.6 to –489.2 steps, p=0.022) and G-HSD group (mean difference –1637 steps, 95% CI –2942.2 to –332.4 steps, p=0.039) compared to the CTR group, with no differences between the two patient groups. Total bed time had non-significant higher average values in the patient groups compared to the controls (hEDS: 529.9 min, G-HSD: 524.3 min, controls: 490.6 min, p=0.082). Other PA variables and sleep parameters did not significantly differ between the groups. When comparing step counts with recommended values (i.e., 7500 steps/day), both patient groups scored significantly lower (p≤0.001, 70% and 81% of the adults with hEDS and G-HSD respectively did not meet the recommended step count), whereas healthy controls did not significantly differ from the recommended values (p=0.277, 58% of the controls did not meet the recommended step count). Sleep efficiency was significantly higher (p≤0.003) compared to the recommended value (85%) in all three groups (80%, 83%, and 90% of the adults with hEDS, G-HSD, and controls respectively met the recommended sleep efficiency).

Patient-reported outcomes

Questionnaire data are shown in Table 4. All variables measured were significantly different between the controls and the two patient groups (all p<0.001), except for anxiety which only showed a tendency toward statistical significance across all three groups (p=0.051). Depression, fatigue, pain impact, kinesiophobia, sleepiness, and pain medication were significantly higher in both patient groups compared to controls (p≤0.023), while subjectively scored sleep quality and quality of life [physical health component summary score (PCS) and mental health component summary score (MCS)] were significantly lower (p≤0.003). No differences were observed between the hEDS and G-HSD group on any variable.

Relationship between main PA and sleep parameters, and participant characteristics and patient-reported outcomes

Table 5 shows the correlations between step counts or sleep efficiency, and age, BMI, and patient-reported

Table 2: Participant characteristics

	hEDS (n=20)	G-HSD (n=23)	CTR (n=32)	P value
Age (years)	34.5 [24.0–52.0]	30.0 [23.0–41.0]	33.5 [22.3–42.3]	**0.386**
BMI (kg/m²)	24.1 [19.4–31.7]	26.2 [24.0–29.2]	23.8 [20.9–29.1]	**0.258**
GJH (Beighton/9)	6.0 [5.0–7.0]	6.0 [5.0–7.0]	1.0 [0.0–3.0]	**<0.001***
Painful body surface area (Margolis, %)	25.7 [20.9–31.1]	31.3 [11.8–50.1]	1.0 [0.0–3.7]	**<0.001***
Profession				**0.338**
Homemaker	2 (10.5%)	3 (13%)	1 (3.2%)	
Physical worker	1 (5.3%)	3 (13%)	1 (3.2%)	
Employee (sedentary worker)	8 (42.1%)	10 (43.5%)	15 (48.4%)	
Liberal profession	2 (10.5%)	0 (0%)	0 (0%)	
Other	6 (31.6%)	7 (30.4%)	14 (45.2%)	
Current working status				**<0.001***
Student	3 (16.7%)	3 (14.3%)	9 (29%)	
Employed	4 (22.2%)	7 (33.3%)	20 (64.5%)	
Homemaker	2 (11.1%)	1 (4.8%)	2 (6.5%)	
Sick leave	9 (50%)	10 (47.6%)	0 (0%)	
Education				**0.223**
Lower secondary education	2 (10.5%)	1 (4.3%)	0 (0%)	
Higher secondary education	3 (15.8%)	7 (30.4%)	5 (16.1%)	
Higher education	14 (73.7%)	15 (65.2%)	26 (83.9%)	
Marital status				**0.528**
Single	8 (42.1%)	9 (39.1%)	13 (41.9%)	
Married	6 (31.6%)	7 (30.4%)	13 (41.9%)	
Divorced	2 (10.5%)	0 (0%)	1 (3.2%)	
Living together	3 (15.8%)	7 (30.4%)	4 (12.9%)	

Data are shown as median [quartile 1–quartile 3] or frequencies (absolute number and %); BMI: Body mass index; GJH: generalized joint hypermobility; hEDS: hypermobile Ehlers–Danlos syndrome; G-HSD: generalized hypermobility spectrum disorder; CTR: control group; liberal profession: an occupation pursued in relation to an ideal of public service and requiring substantial mastery of complex skills in the liberal arts or sciences (includes lawyers, engineers, doctors, dentists, notaries, among others); lower secondary education: until 15y; higher secondary education: until 18y; higher education: >18y, *: P value < 0.05.

Table 3: Physical activity and sleep

	hEDS	G-HSD	CTR	P value
Physical activity	(n=20)	(n=21)	(n=31)	
Wearing time (min)	842.2 ± 60.01	833.9 ± 104.27	862.8 ± 48.31	**0.329**
Valid days (days/week)	6.9 ± 0.31	6.7 ± 0.88	6.9 ± 0.36	**0.393**
Step counts (n/day)	5233.5 ± 2485.52	5409.6 ± 2193.27	7046.9± 2280.41	**0.010***
MVPA (min/day)	74.7 ± 30.95	80.5 ± 28.88	89.1 ± 26.98	**0.207**
Moderate (min/day)	65.7 ± 27.16	71.5 ± 25.42	78.1 ± 23.83	**0.228**
Vigorous (min/day)	7.2 ± 4.43	7.1 ± 4.19	8.7 ± 5.06	**0.375**
Very vigorous (min/day)	1.9 ±1.12	1.9± 0.94	2.3 ± 2.01	**0.498**

Table 3: *(Continued)*

	hEDS	G-HSD	CTR	P value
Sleep	(n=20)	(n=23)	(n=31)	
Sleep efficiency (%)	88.3 ± 4.23	88.5 ± 3.68	89.2 ± 4.16	**0.700**
Number of awakenings	16.8 ± 6.20	17.4 ± 5.51	17.4 ± 5.77	**0.921**
Latency (min)	8.8 ± 6.94	9.2 ± 6.75	6.9 ± 3.61	**0.312**
TBT (min)	529.9 ± 86.57	524.3 ± 72.06	490.6 ± 42.49	**0.082**
TST (min)	467.3 ± 86.62	463.3 ± 60.86	438.0 ± 38.02	**0.193**
WASO (min)	53.8 ± 18.61	51.9 ± 21.59	45.7 ± 20.06	**0.339**

Data are shown as mean ± standard deviation. All variables are means calculated over seven days, except for number of valid days. hEDS: hypermobile Ehlers–Danlos syndrome; G-HSD: generalized hypermobility spectrum disorder; CTR: control group; n= number of participants; wearing time: time that the physical activity tracker was worn between 7:00 AM and 10:00 PM; valid days: number of valid days (≥8 hours of physical activity tracker wearing time); MVPA: moderate to vigorous physical activity; TBT: total bed time; TST: total sleep time; WASO: wake after sleep onset; *: P value < 0.05.

Table 4: Patient-reported outcome scores of participants

	hEDS (n=20)	G-HSD (n=23)	CTR (n=32)	P value
Anxiety (HADS/21)°	5.3 ± 3.38	6.4 ± 3.21	4.1 ± 3.73	**0.051**
Depression (HADS/21)°	6.6 ± 2.97	6.6 ± 3.57	2.6 ± 2.59	**<0.001***
Fatigue (CIS/140)°	81.7 ± 13.64	90.5 ± 13.91	61.0 ± 24.58	**<0.001***
Pain impact (MPI/30)	17.1 ± 2.80	17.0 ± 4.40	8.6 ± 3.24	**<0.001***
Kinesiophobia (TAMPA/68)	39.3 ± 7.20	43.6 ± 8.31	29.0 ± 7.22	**<0.001***
Subjective sleep (/18)°	9.5 ± 3.48	10.0 ± 2.89	6.5 ± 2.89	**<0.001***
Sleepiness (ESS/24)°	11.4 ± 5.91	13.1 ± 4.88	6.6 ± 4.33	**<0.001***
QoL PCS (SF36/400)	117.5 [63.8–145.0]	110.0 [65.0–202.5]	337.5 [281.3–367.5]	**<0.001***
QoL MCS (SF36/400)	252.6 [213.3–275]	229.7 [153.3–310.0]	336.0 [251.2–364.0]	**<0.001***
Pain medication (doses/day)°	0.9 [0.1–2.0]	0.3 [0.0–1.3]	0.0 [0.0–0.0]	**<0.001***

Normal distributed data are shown as mean ± standard deviation, non-normal distributed data as medians [quartile 1–quartile 3]. °: variables of which means calculated over seven days are shown; hEDS: hypermobile Ehlers–Danlos syndrome; G-HSD: generalized hypermobility spectrum disorder; CTR: control group; HADS: hospital anxiety and depression questionnaire; CIS: checklist individual strength; MPI: multidimensional pain inventory; TAMPA: tampa scale for kinesiophobia; ESS: Epworth sleep scale; QoL: quality of life; PCS: physical health component summary score; MCS: mental health component summary score; SF36: RAND 36-item health survey; *: P value < 0.05.

Table 5: Association between primary outcomes and clinical measures in hEDS and G-HSD

	Step counts		Sleep efficiency	
	hEDS (n=20)	G-HSD (n=21)	hEDS (n=20)	G-HSD (n=23)
Age (years)	−0.503*	−0.309	0.087	−0.432*
BMI (kg/m²)	−0.578*	0.080	0.134	−0.398
Beighton (/9)	−0.231	0.092	0.098	−0.118
Sleepiness (ESS)	0.272	0.073	0.065	−0.155
Pain surface (Margolis)	−0.023	−0.456*	0.111	−0.192
Anxiety (HADS)	−0.146	0.116	−0.179	−0.172
Depression (HADS)	−0.462*	−0.136	0.054	−0.341
Fatigue (CIS)	−0.110	−0.176	0.106	−0.012
Pain medication	−0.198	−0.393	−0.239	−0.221
Subjective sleep	−0.238	0.122	0.238	−0.194
Pain impact (MPI)	−0.162	−0.476*	0.193	−0.099
Kinesiophobia	−0.458*	−0.003	−0.238	−0.042

Data shown are Pearson (for normal distributed data) and Spearman (for non-normal distributed data, i.e., pain surface and pain medication) correlation coefficients. hEDS: hypermobile Ehlers–Danlos syndrome; G-HSD: generalized hypermobility spectrum disorder; BMI: body mass index; ESS: Epworth sleep scale; HADS: hospital anxiety and depression questionnaire; CIS: checklist individual strength; MPI: multidimensional pain inventory; *: P value < 0.05.

outcomes in both patient groups. Moderate statistically significant inverse correlations were found between step counts and age, BMI, depression, and kinesiophobia in the hEDS group ($p<0.05$ for all). In the G-HSD group, moderate statistically significant inverse correlations were identified between step counts and pain surface and psychosocial pain impact ($p=0.038$ and $p=0.029$, respectively).

All outcomes with significant correlations with step counts were included in the backward stepwise regression analysis (see Supplementary Tables A1 and A2). No multicollinearity problems were identified (all VIF<2.5). Regression analysis showed that the variance in BMI and kinesiophobia [TAMPA scale for Kinesiophobia (TSK score)] significantly explained 52.6% of the variance in step counts in the hEDS group. In the G-HSD group, 18.5% of the variance in step counts could be attributed to variance in pain impact [multidimensional pain inventory (MPI score)].

Table A1: Backward stepwise regression analysis with step counts as the dependent variable in the hEDS group

Variables°	B	SE	β	t	p
BMI (kg/m²)	−219.84	58.82	−0.61	−3.74	0.002*
Kinesiophobia	−181.37	54.40	−0.55	−3.33	0.004*

°Only significant correlates were included in the model, *significant when $p<0.05$, B = unstandardized coefficient, SE = standard error, β = standardized coefficient, BMI = body mass index.

Table A2: Backward stepwise regression analysis with step counts as the dependent variable in the G-HSD group

Variables°	B	SE	β	t	p
Pain impact (MPI)	−242.38	102.87	−0.48	−2.36	0.029*

°Only significant correlates were included in the model, *significant when $p<0.05$, B = unstandardized coefficient, SE = standard error, β = standardized coefficient.

Regarding sleep, no significant correlations were found, except for a significant negative correlation between sleep efficiency and age in G-HSD ($r=-0.432$, $p=0.040$). Therefore, no backward stepwise regression analysis was performed.

DISCUSSION

This was the first study that objectively evaluated PA and sleep measures in adults with hEDS and G-HSD diagnosed according to the most recent diagnostic criteria, in comparison with a matched healthy control group and recommended values. Moreover, this study also determined contributors to PA in these patient groups. The results indicate that hEDS and G-HSD patients had a significantly lowered PA level, demonstrated by a lower step count number compared to controls and compared to the recommended 7500 steps per day ("somewhat active"). This study could not show significant objective differences between the three groups regarding sleep parameters, although patients subjectively scored their sleep quality as impaired. Second, this study determined that patient characteristics (BMI and age) and symptoms of depression and kinesiophobia were inversely correlated with step count number in the hEDS group, of which BMI and kinesiophobia explained more than half of the variance in step counts. In the G-HSD group, pain factors (painful surface and pain impact) were inversely correlated with step count number, of which 18.5% of the variance could be attributed to variance in pain impact. No contributors for sleep could be identified in the patient groups.

Physical activity

This study showed that objectively measured PA is reduced in adults with hEDS and G-HSD, demonstrated by 75% of this population which did not meet the recommended 7500 steps and had lower daily step counts in comparison with controls. These results are in accordance with previous research using patient-reported questionnaires, which identified lower habitual PA and level of sport activities and poor PA levels with 50% of the patients being inactive. Furthermore, this is in line with the observed reduced ambulation, daily living and sport activities in hypermobile patient populations [5, 8–10, 54].

By contrast, we could not identify any differences in MVPA between the three groups. This is different from patients with rheumatoid arthritis (RA) and fibromyalgia, who show lower levels of MVPA compared to controls, although these pathologies are both chronic musculoskeletal disorders with several clinical similarities with hEDS and G-HSD [55, 56]. We could hypothesize that adults with hEDS and G-HSD avoid walking, whereas they still perform many other activities, including exercises and physiotherapy—in which hypermobile patients frequently engage with [57, 58]. However, to our knowledge, there are no other studies concerning objective PA measurements in adults with hEDS and G-HSD with which we can compare our results. Therefore, our hypothesis should be interpreted with caution.

The present study showed that age, BMI, symptoms of depression, and kinesiophobia were moderately associated with objectively measured PA (step counts) in individuals with hEDS. Similar to the general healthy population, age and BMI were inversely associated with PA [59, 60]. The inverse correlation between symptoms of depression and PA could be attributed to both psychological and physiological mechanisms such as increased levels of serotonin and dopamine, increased endorphin secretion, improved self-esteem and self-

efficacy, and distraction from stressful stimuli when increasing PA [61]. This study identified kinesiophobia as a contributor to the decreased PA levels seen in adults with hEDS, which has previously also been hypothesized by Rombaut et al. (2010) [5]. Decreased PA in adults with hEDS could partially be explained by the fear avoidance model, in which injuries or pain during daily activities takes on negative value and becomes a conditioning stimulus, resulting in avoidance of these activities [62].

In the G-HSD group, pain surface and (psychosocial) impact of pain were inversely related with PA (step counts). Furthermore, in these patients pain impact could be identified as a determinant for PA, implying that a higher psychosocial impact of pain resulted in lower daily step counts. This is in accordance with previous research in patient populations with RA and fibromyalgia, showing associations between higher reported pain and lower PA levels [20, 63, 64].

Consequently, we can suggest that individuals with hEDS and G-HSD have reduced step count numbers, which could partly be attributed to fear of having pain in the hEDS group, and to the impact of pain in the G-HSD group. Surprisingly, fatigue did not contribute to the reduced PA in patients with hEDS/G-HSD. Furthermore, it was unexpected that pain did not come up as a contributing factor to reduced PA in hEDS. However, our results should be interpreted with caution because correlations had moderate strength and only 18% of the variance of PA in G-HSD could be explained by the psychosocial impact of pain in the linear regression model.

Sleep

This study showed conflicting results regarding subjectively and objectively measured sleep parameters. Results of the questionnaires showed that patients perceive lower sleep quality and report feeling sleepier during the day. However, excessive sleepiness (ESS≥16) could not be identified [65]. Furthermore, objective measurements (accelerometry) did not show many significant differences between patients with hEDS/G-HSD and controls. Whereas total bed time was on average 30 minutes higher per night in the patient groups compared to the control group, this difference did not meet statistical significance. Furthermore, sleep efficiency met the recommendations for good sleep quality (total sleep time/total bed time≥85%) and a recommended total sleep time of 7 hours or more each night was achieved, on average, in all groups [51, 66].

By contrast, previous research in subjects with EDS showed a higher prevalence of obstructive sleep apnea measured by polysomnography or respiratory polygraphy [14, 16, 18]. However, to our knowledge, no other studies concerning sleep measured by accelerometry in adults with hEDS and G-HSD have been performed with which we can compare our results. On the other hand, our subjective sleep results of impaired subjective sleep quality evaluated by questionnaires are in line with previous studies [7, 15, 16, 19, 67]. We can conclude that, although individuals with hEDS and G-HSD perceive more fatigue and poor sleep quality, sleep might not be impaired in adults with hEDS and G-HSD based on objective parameters. This difference between objective and subjective results could be due to the fact that, when assessing sleep, the loss of consciousness during sleep makes it hard to self-observe sleep behavior [51]. Furthermore, orthostatic intolerance in hypermobile adults could also explain the feeling of being more fatigued [68, 69]. Finally, the difference in subjective sleep outcomes between patients and controls could be partially explained by the higher anxiety and depression in these patient groups. However, these conclusions should be interpreted with caution as polysomnography remains the golden standard for sleep measurements and could additionally identify sleep disordered breathing. Moreover, for sleep measurements based on accelerometry, currently no normative adult values exist, which makes it difficult to interpret these results [70].

hEDS versus G-HSD

No differences in PA, sleep, and clinical symptoms (pain, pain medication, sleepiness, quality of life, kinesiophobia, anxiety, depression, and fatigue) were found between the two patient groups (hEDS and G-HSD). Although this study showed that determinants of PA in the two patient groups differ, both can be traced back to the consequences of their experienced pain. In accordance with Hakim et al. (2019), these findings demonstrate that hEDS and G-HSD share many similar symptoms and comorbidities [71]. As such, Copetti et al. (2019) have previously suggested that the distinction between hEDS and HSD based on the current nosology does not reflect differences in the severity of all symptoms and comorbidities [72]. Based on the symptom profile, it is therefore inaccurate to regard G-HSD as a less severe pathology than hEDS. Although these patient groups differ with respect to soft tissue fragility and skin issues, patients in both groups require an individually adjusted treatment plan for their symptoms and co morbidities [3].

Clinical implications

This study showed that individuals with hEDS and G-HSD take less steps on a daily basis and do not meet the recommended international criteria for daily physical activity. As there is an inverse relationship of daily steps with important health outcomes in the general population such as all-cause mortality and cardiovascular events, improving daily steps could have health benefits in these patient groups [52, 73]. Furthermore, physical activity such as walking is essential for bone health,

which has shown to be impaired in some individuals with hEDS/HSD [74]. Based on our data regarding determinants of PA, targeting fear-avoidance beliefs and pain in individuals with hEDS and G-HSD could be recommended [75]. Several treatments evaluating cognitive behavior therapy (CBT) and graded activity exposure have already shown evidence to improve fear-avoidance beliefs in patients with fibromyalgia [76–78]. However, only one small cohort study has evaluated this treatment option in individuals with symptomatic hypermobility, demonstrating positive outcomes [79]. Therefore, future studies should focus on evaluating treatments incorporating CBT, graded activity exposure, and pain relief in individuals with hEDS and G-HSD.

Limitations and strengths

To the best of our knowledge, this is the first study objectively evaluating PA and sleep in hEDS and G-HSD according to the new diagnostic criteria. Moreover, this study evaluated differences in PA, sleep, and clinical features between these two patient groups and determined contributors to PA. However, some limitations have to be considered when interpreting these results. First, sedentary time and light physical activity could not be determined as no cut-offs exist for adults based on the vector magnitude (tri-axial counts). Second, objectively and subjectively measured sleep parameters were analyzed based on self-reported bed and wake time and with three non-validated sleep questions, respectively, which could compromise the accuracy of the sleep analyses. Finally, selection bias could be considered as our control group had relatively low activity levels. However, current research shows that 40–50% of the healthy Belgian population are inactive and accelerometers are known to underestimate step count number [80–82]. Nevertheless, this underestimation did not affect the differences in step count between the three groups (hEDS, G-HSD, and controls).

CONCLUSION

This study objectively assessed PA and sleep in adults with hEDS/G-HSD. No differences in objectively measured sleep parameters were identified, although patients scored their sleep quality as impaired. Furthermore, our results demonstrated that adults with hEDS and G-HSD were less active and had lower step counts than healthy peers, which may be partially due to kinesiophobia and the impact of pain, respectively. Therefore, treatment focusing on fear-avoidance beliefs and pain relief has sound clinical reasoning to likely result in increased daily step counts, which may further benefit overall health in these hypermobile patients.

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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